FDA Statistical Review and Evaluation

Document for the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

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Menactra, Meningococcal (Groups A, C, Y, and W135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

Indication: active immunization of adolescents and adults 11 to 55 years of age for prevention of invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, Y, and W-135.

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1. Introduction

In the application for licensure, Aventis Pasteur (AP) has submitted information from several clinical trials. In these trials, AP used the name TetraMenD for this product. It will be the name used in this report as well.

In order to infer efficacy based on immune response, the primary immunogenicity hypothesis was non-inferiority of TetraMenD conjugate vaccine with respect to Menomune polysaccharide vaccine, as measured by the percentage of participants with a 4-fold rise in serum bactericidal assay with baby rabbit complement (SBA-BR) titer. The data are in the form of reciprocal serum dilutions.

The criteria used by AP in demonstrating non-inferiority is that the upper limit of the two-sided 95% confidence interval of the difference between the two groups in the proportions of subjects presenting a ? 4-fold rise from baseline in SBA-BR titers (proportion in Menomune minus the proportion in TetraMenD) being less than 10 percentage points.

2. Comparison of SBA-BR and SBA-HC

Since the current standard for seroprotection is based on the serum bactericidal assay with human complement (SBA-HC) titers ?1:4 or HC titers ?1:8 for serogroup C, AP has provided the results of a supplemental study in which the two assay methods were performed on sera from subsets of subjects from two clinical trials: MTA02 (11 to 18 yrs) and MTA09 (18 to 55 yrs).

In the original submission, AP presented results of the primary analyses using geometric mean titer (GMTs), reverse cumulative distribution curves (RCDC), and seroprotection rates for serogroups C, Y, and W-135. The results of serogroup A are submitted later in an amendment to the original BLA submission.

Note: The values of HC titers in serogroups C, Y, and W-135 are multiples of 2. However, perhaps due to interpolation, the values of HC titers in serogroup A were not multiples of 2, thus unlike those of other serogroups.

2.1. AP's Results

?? Seroprotection Rates:

Table 2.1.1. Comparison of SBA-BR 4-fold Rise in Titer with SBA-HC Titer on Day 28 for Subjects with Both Measurements in all Serogroups in Studies MTA02 and MTA09.

Study & Serogroup	Menomune			TetraMenD		
	SBA-BR	SBA-HC		SBA-BR	SBA-HC	
	?4-fold Rise	Titer ? 1:4	Titer ? 1:8	?4-fold Rise	Titer ? 1:4	Titer ? 1:8
02A	51/52 (98%)	50/52 (96%)	46/52 (88%)	44/50 (88%)	47/50 (94%)	40/50 (80%)
02C	73/81 (90%)	70/81 (86%)	62/81 (77%)	75/84 (89%)	79/84 (94%)	77/84 (92%)
02Y	50/62 (81%)	59/62 (95%)	59/62 (95%)	61/65 (94%)	61/65 (94%)	61/65 (94%)
09Y	36/50 (72%)	50/50 (100%)	50/50 (100%)	40/50 (80%)	48/50 (96%)	48/50 (96%)
02W	56/58 (97%)	54/58 (93%)	53/58 (91%)	59/61 (97%)	60/61 (98%)	58/61 (95%)
09W	47/50 (94%)	50/50 (100%)	49/50 (98%)	48/50 (96%)	50/50 (100%)	49/50 (98%)

Table 2.1.2. Seroprotection Rates for the Naïve Subjects (subjects with baseline SBA-HC titers < 1:4) of the Subset with Both Titer Values.

Study & Serogroup	Menomune			TetraMenD		
	SBA-BR	SBA-HC		SBA-BR	SBA-HC	
	?4-fold Rise	Titer ? 1:4	Titer ? 1:8	?4-fold Rise	Titer ? 1:4	Titer ? 1:8
02A	11/11 (100%)	10/11 (91%)	9/11 (82%)	12/12 (100%)	11/12 (92%)	8/12 (67%)
02C	56/62 (90%)	51/62 (82%)	43/62 (69%)	54/57 (95%)	52/57 (91%)	50/57 (88%)
02Y	35/39 (90%)	36/39 (92%)	36/39 (92%)	38/41 (93%)	38/41 (93%)	38/41 (93%)
09Y	15/17 (88%)	17/17 (100%)	17/17 (100%)	18/18 (100%)	16/18 (89%)	16/18 (89%)
02W	23/23 (100%)	19/23 (83%)	18/23 (78%)	21/22 (95%)	21/22 (95%)	19/22 (86%)
09W	8/9 (89%)	9/9 (100%)	8/9 (89%)	8/8 (100%)	8/8 (100%)	8/8 (100%)

?? Geometric Mean Titers (GMTs):

Table 2.1.3. Comparison of the Geometric Mean Titers (GMTs) on Day 28 for Serogroup A from Subjects who Had Both Measurements.

02A	Menomune			TetraMenD		
	N	GMT	95% CI	N	GMT	95% CI
Day 0	52	51.71	28.19, 94.86	50	119.43	67.31, 211.91
Day 28	52	2568.88	1848.85, 3569.32	50	4096.00	3087.71, 5433.55

?? Reverse Cumulative Distribution Curves (RCDCs):

Please see the Appendix for RCDC figures from AP's documents.

2.2 AP's Conclusion

1. For serogroups C, Y, and W-135:

?? The concordance observed in the bactericidal response patterns between the human complement assay (SBA-HC) results and the rabbit complement assay (SBA-BR) results in a subset comparison confirms the reliability of the SBA-BR for evaluating protective immune responses to serogroups C, Y, and W-135 meningococcal vaccines.
- o A comparison of the rate of 4-fold rise in titer by SBA-BR to the rate of achieving a titer of ? 1:4 by SBA-HC between the TetraMenD and Menomune groups was favorably demonstrated for serogroups C, W-135, and Y.
- o Both sets of RCDCs (SBA-BR and SBA-HC) overlap for the two vaccine groups from both clinical results for serogroups C, Y, and W-135.
- o The agreement in the seroconversion rates measured by the fold rise in SBA-BR titers to the proportion of subjects having post-vaccination titers above the putative protective level (? 1:4 or more conservatively ? 1:8), coupled to the overlapping RCDC (SBA-BR and SBA-HC) provides strong evidence that the SBA-BR yields reliable results for assessing non-inferiority between the TetraMenD conjugate vaccine and the licensed polysaccharide vaccine Menomune.

2. For serogroup A:

?? The proportion of subjects achieving a ? 4-fold rise in titer by SBA-BR was similar to the proportion of subjects achieving a titer of ? 1:4 by SBA-HC between the TetraMenD and Menomune groups for serogroup A.

?? Both sets of Day 28 RCDCs (SBA-BR and SBA-HC) have a similar profile for the two vaccine groups for serogroup A.
?? The agreement in the seroconversion rates measured by the fold rise in SBA-BR titers to the proportion of subject having post-vaccination titers above the putative protective level (SBA-HC titer ? 1:4), coupled to the similar RCDCs (SBA-BR and SBA-HC) provides strong evidence that the SBA-BR yields relevant results for assessing non-inferiority between the TetraMenD conjugate vaccine and the licensed polysaccharide vaccine Menomune for response to serogroup A.
?? By analogy with the correlate of immunity established for serogroup C, these data provide support for extrapolation of AP results demonstrateing a ? 4-fold rise in SBA-BR titer to protection against serogroup A.

2.3. Reviewer's Comments on AP's Results

1. The reverse cumulative distribution curves (RCDCs) were provided and they are included as an attachment. The conclusions drawn from these RCDCs are by visual comparisons only.

2. The results presented are all descriptive in nature. No statistical analysis was provided by AP.

2.4. Reviewer's Analyses

?? Seroprotection Rates:

Table 2.4.1. Results from an Analysis of Differences in the Seroprotection Rates between Menomune and TetraMenD from all Three Criteria*

Study	Criteria	Menomune		TetraMenD		Diff (M-T)	p-value	95% CI
		N	Proportion	N	Proportion			
02A	BR?4fold	52	0.98	50	0.88	0.10	0.054	-0.002, 0.224
	HC?1:4	52	0.96	50	0.94	0.02	0.723	-0.078, 0.132
	HC?1:8	52	0.88	50	0.80	0.08	0.270	-0.067, 0.240
02C	BR?4fold	81	0.90	84	0.89	0.01	0.924	-0.091, 0.108
	HC?1:4	81	0.86	84	0.94	-0.08	0.106	-0.177, 0.017
	HC?1:8	81	0.77	84	0.92	-0.15	0.008	-0.267, -0.031
02Y	BR?4fold	62	0.81	65	0.94	-0.13	0.026	-0.260, -0.015
	HC?1:4	62	0.95	65	0.94	0.01	0.834	-0.080, 0.110
	HC?1:8	62	0.95	65	0.94	0.01	0.834	-0.080, 0.110
09Y	BR?4fold	50	0.72	50	0.80	-0.08	0.508	-0.251, 0.091
	HC?1:4	50	1.00	50	0.96	0.04	0.209	-0.034, 0.137
	HC?1:8	50	1.00	50	0.96	0.04	0.209	-0.034, 0.137
02W	BR?4fold	58	0.97	61	0.97	-0.00	1.000	-0.090, 0.083
	HC?1:4	58	0.93	61	0.98	-0.05	0.159	-0.152, 0.029
	HC?1:8	58	0.91	61	0.95	-0.04	0.549	-0.146, 0.063
09W	BR?4fold	50	0.94	50	0.96	-0.02	0.751	-0.130, 0.084
	HC?1:4	50	1.00	50	1.00	0.00	1.000	-0.073, 0.072
	HC?1:8	50	0.98	50	0.98	0.00	1.000	-0.088, 0.088

* P-values and exact 2-sided 95% confidence intervals (CI) obtained from the ---------- --- software.

Comments:

1. In non-inferiority comparisons, the upper confidence bounds of the 95% CI are required to be within 10 percentage points. However, the sample size is not sufficient for testing the non-inferiority hypothesis with regard to the two assay methods.

2. Except for serogroup A, the upper bounds of the 95% CI on the difference in proportions are under 15%.

3. Except for serogroup Y in study MTA02, all results show general agreement between the conclusions drawn from HC or BR assays.

?? Geometric Mean Titers:

Table 2.4.2. GMTs for Both Methods and for All 4 Serogroups*

(a) SBA-BR

Study		Menomune			TetraMenD		
		N	GMT	95% CI	N	GMT	95% CI
02A	Day 0	52	51.71	27.77, 96.27	50	119.43	66.34, 215.00
	Day 28	52	2568.88	1834.13, 3597.96	50	4096.00	3065.70, 5472.55
02C	Day 0	81	39.30	24.82, 62.21	84	30.96	20.03, 47.86
	Day 28	81	1682.10	1219.37, 2320.43	84	1736.42	1265.44, 2382.70
02Y	Day 0	62	125.17	86.08, 182.01	65	77.54	49.86, 120.59
	Day 28	62	1184.18	893.43, 1569.57	65	1471.50	1053.54, 2055.29
09Y	Day 0	50	85.63	43.99, 166.68	50	133.44	76.50, 232.75
	Day 28	50	1428.22	862.98, 2363.67	50	1910.85	1215.42, 3004.18
02W	Day 0	58	30.51	20.28, 45.88	61	26.38	17.28, 40.26
	Day 28	58	1364.16	974.57, 1909.48	61	1345.05	998.88, 1811.18
09W	Day 0	50	39.40	24.15, 64.27	50	29.04	18.58, 45.40
	Day 28	50	2225.63	1589.13, 3117.07	50	1640.59	1200.94, 2241.19

(b) SBA-HC

Study		Menomune			TetraMenD		
		N	GMT	95% CI	N	GMT	95% CI
02A	Day 0	52	6.25	4.80, 8.15	50	5.86	4.58, 7.48
	Day 28	52	18.65	14.27, 24.38	50	17.88	13.35, 23.94
02C	Day 0	81	2.44	2.24, 2.65	84	2.71	2.44, 3.02
	Day 28	81	29.88	19.38, 46.09	84	46.39	32.20, 66.83
02Y	Day 0	62	6.26	4.06, 9.63	65	5.57	3.85, 8.04
	Day 28	62	108.24	70.52, 166.13	65	118.79	75.63, 186.58
09Y	Day 0	50	21.11	11.67, 38.20	50	18.64	10.81, 32.13
	Day 28	50	216.77	132.59, 354.39	50	139.10	89.20, 216.92
02W	Day 0	58	14.54	8.62, 24.52	61	15.46	9.58, 24.96
	Day 28	58	89.43	58.37, 137.03	61	79.42	55.89, 112.86
09W	Day 0	50	21.41	13.43, 34.11	50	27.47	17.18, 43.94
	Day 28	50	85.63	59.32, 123.61	50	99.73	66.11, 150.46

* For serogroup A, the values for the 95% CI obtained from the ------- software are different from those provided by AP. This difference is due to ------- using the t-distribution instead of the normal distribution in calculating the confidence intervals.

?? Analysis of Covariance on GMTs with Treatment and Baseline as Covariates:

Table 2.4.3. Results of Analysis of Covariance Performed on the Log (Base 2) Transformed Titers with Treatment group and Transformed Baseline Titers as Covariates*

Study	Assay	Covariate	Coeff.[1]	95% CI	p-value	Ratio[2]	95% CI of ratio[3]
02A	BR	Treatment	-0.46	-1.07, 0.15	0.14	0.73	0.47, 0.90
		Baseline	0.18	0.08, 0.27	0.00		
	HC	Treatment	0.01	-0.49, 0.51	0.96	1.09	0.71, 1.43
		Baseline	0.51	0.32, 0.70	0.00		
02C	BR	Treatment	-0.12	-0.74, 0.49	0.70	0.92	0.60, 1.41
		Baseline	0.22	0.12, 0.33	0.00		
	HC	Treatment	-0.45	-1.23, 0.33	0.26	0.73	0.42, 1.26
		Baseline	1.19	0.57, 1.81	0.00		
02Y	BR	Treatment	-0.55	-1.12, 0.02	0.06	0.68	0.46, 1.01
		Baseline	0.34	0.22, 0.46	0.00		
	HC	Treatment	-0.19	-1.04, 0.66	0.66	0.88	0.48, 1.58
		Baseline	0.34	0.15, 0.52	0.00		
09Y	BR	Treatment	-0.20	-1.07, 0.68	0.66	0.87	0.48, 1.60
		Baseline	0.35	0.21, 0.49	0.00		
	HC	Treatment	0.58	-0.28, 1.43	0.18	1.49	0.82, 2.70
		Baseline	0.36	0.21, 0.51	0.00		
02W	BR	Treatment	-0.05	-0.63, 0.52	0.86	0.96	0.65, 1.44
		Baseline	0.34	0.21, 0.46	0.00		
	HC	Treatment	0.20	-0.48, 0.89	0.55	1.15	0.72, 1.85
		Baseline	0.39	0.26, 0.51	0.00		
09W	BR	Treatment	0.36	-0.28, 0.99	0.27	1.28	0.82, 1.99
		Baseline	0.19	0.06, 0.32	0.01		
	HC	Treatment	-0.08	-0.78, 0.62	0.82	0.94	0.58, 1.54
		Baseline	0.38	0.23, 0.53	0.00		

* The analysis was performed with the software Stata version-8.

Notes:

1. The coefficient for treatment was calculated using TetraMenD as the reference. It is equivalent to testing the difference of the mean log base 2 titer of Menomune minus the mean log base 2 titer of TetraMenD, after adjusting for the baseline titers.

2. The ratios were calculated by taking the antilog (base 2) of the coefficients for treatment from the ANCOVA results.

3. The 95% confidence limits for the ratios were obtained by taking the antilog (base 2) of the 95% confidence limits on the treatment coefficients.

4. From the results above, it is clear that the baseline titer plays an important role in predicting the final titer for a subject (baseline p-values are all very small).

5. Again, because of how the ratios were defined, only the upper confidence limits are used to evaluate non-inferiority of Menomune compared to TetraMenD. The upper bounds on the ratios of Menomune to TetraMenD are all under 2, except for study 09 with the HC assay, where the upper bound is 2.70.

?? Sensitivity and Specificity: a Paired Analysis

In general, when a new method is compared to a "gold standard", sensitivity is the proportion of the subjects correctly classified as "positive" by the new method among the group of subjects defined as "positive" by the "gold standard." Specificity is the proportion of the subjects correctly classified as "negative" by the new method among the group of subjects defined as "negative" by the "gold standard." When sensitivity and specificity are both one, it means the new method is exactly as good as the "gold standard."

To compare the BR and HC methods using paired data, sensitivity and specificity of the BR assay was investigated by treating the HC assay as the "gold standard." In this setting, sensitivity of the BR assay is the proportion of the subjects who are classified as seroprotected by the BR method out of the ones classified as seroprotected by the HC method. Specificity is the proportion of the subjects who are classified as not seroprotected by the BR method out of the ones classified as not seroprotected by the HC method.

It is difficult to interpret the cases of 0/0, which indicates that no subject is classified in that category by either method. Such result could be due to the small sample sizes of these studies.

Table 2.4.4 Results from Direct Comparison of SBA-BR to SBA-HC using SBA-HC as the "Gold Standard" (includes comparisons of the BR ? 4-fold rise with HC ? 1:4 and HC ? 1:8 at day 28, as well as comparisons of BR ? 1:128, BR ? 1:256 with HC ? 1:4, HC? 1:8 at both day 0 and day 28)

(a) BR ? 4-fold rise vs HC ? 1:4 at day 28

Study	Vaccine	BR+ within HC+	Sensitivity	BR- within HC-	Specificity
02A	Menomune	49/50	0.98	0/2	0.00
	TetraMenD	42/47	0.89	1/3	0.33
02C	Menomune	63/70	0.90	1/11	0.09
	TetraMenD	70/79	0.89	0/5	0.00
02Y	Menomune	48/59	0.81	1/3	0.33
	TetraMenD	57/61	0.93	0/4	0.00
09Y	Menomune	36/50	0.72	0/0	?
	TetraMenD	38/48	0.79	0/2	0.00
02W	Menomune	52/54	0.96	0/4	0.00
	TetraMenD	58/60	0.97	0/1	0.00
09W	Menomune	47/50	0.94	0/0	?
	TetraMenD	48/50	0.96	0/0	?

(b) BR ? 4-fold rise vs HC ? 1:8 at day 28

Study	Vaccine	BR+ within HC+	Sensitivity	BR- within HC-	Specificity
02A	Menomune	45/46	0.98	0/6	0.00
	TetraMenD	36/40	0.90	2/10	0.00
02C	Menomune	55/62	0.89	1/19	0.05
	TetraMenD	68/77	0.88	0/7	0.00
02Y	Menomune	48/59	0.81	1/3	0.33
	TetraMenD	57/61	0.93	0/4	0.00
09Y	Menomune	36/50	0.72	0/0	?
	TetraMenD	38/48	0.79	0/2	0.00
02W	Menomune	51/53	0.96	0/5	0.00
	TetraMenD	56/58	0.96	0/3	0.00
09W	Menomune	46/49	0.94	0/1	0.00
	TetraMenD	47/49	0.96	0/1	0.00

(c) BR ? 1:128 vs HC ? 1:4 at day 0

Study	Vaccine	BR+ within HC+	Sensitivity	BR- within HC-	Specificity
02A	Menomune	24/41	0.58	10/11	0.91
	TetraMenD	30/38	0.79	8/12	0.67
02C	Menomune	7/19	0.37	41/62	0.66
	TetraMenD	11/27	0.41	42/57	0.74
02Y	Menomune	18/23	0.78	19/39	0.49
	TetraMenD	16/24	0.67	18/41	0.44
09Y	Menomune	22/33	0.67	12/17	0.70
	TetraMenD	22/32	0.69	9/18	0.50
02W	Menomune	12/35	0.34	19/23	0.83
	TetraMenD	11/39	0.28	17/22	0.77
09W	Menomune	14/41	0.34	4/9	0.44
	TetraMenD	14/42	0.33	6/8	0.75

(d) BR ? 1:128 vs HC ? 1:8 at day 0

Study	Vaccine	BR+ within HC+	Sensitivity	BR- within HC-	Specificity
02A	Menomune	16/19	0.84	24/33	0.73
	TetraMenD	18/20	0.90	14/30	0.47
02C	Menomune	2/4	0.50	51/77	0.66
	TetraMenD	2/10	0.20	50/74	0.68
02Y	Menomune	17/22	0.77	19/40	0.48
	TetraMenD	16/24	0.67	18/41	0.44
09Y	Menomune	22/33	0.67	12/17	0.70
	TetraMenD	22/32	0.69	9/18	0.50
02W	Menomune	11/31	0.35	2/27	0.07
	TetraMenD	7/34	0.20	18/27	0.67
09W	Menomune	14/39	0.36	6/11	0.54
	TetraMenD	14/40	0.35	8/10	0.80

(e) BR ? 1:256 vs HC ? 1:4 at day 0

Study	Vaccine	BR+ within HC+	Sensitivity	BR- within HC-	Specificity
02A	Menomune	22/41	0.54	10/11	0.91
	TetraMenD	23/38	0.60	9/12	0.75
02C	Menomune	6/19	0.32	49/62	0.79
	TetraMenD	11/27	0.41	46/57	0.81
02Y	Menomune	15/23	0.65	28/39	0.72
	TetraMenD	12/24	0.50	27/41	0.66
09Y	Menomune	17/33	0.52	13/17	0.76
	TetraMenD	19/32	0.59	11/18	0.61
02W	Menomune	6/35	0.17	21/23	0.91
	TetraMenD	5/39	0.13	21/22	0.95
09W	Menomune	8/41	0.20	6/9	0.67
	TetraMenD	8/42	0.19	7/8	0.88

(f) BR ? 1:256 vs HC ? 1:8 at day 0

Study	Vaccine	BR+ within HC+	Sensitivity	BR- within HC-	Specificity
02A	Menomune	14/19	0.74	24/33	0.73
	TetraMenD	15/20	0.75	19/30	0.63
02C	Menomune	2/4	0.50	60/77	0.78
	TetraMenD	2/10	0.20	54/74	0.73
02Y	Menomune	15/22	0.68	29/40	0.72
	TetraMenD	12/24	0.50	27/41	0.66
09Y	Menomune	17/33	0.52	13/17	0.76
	TetraMenD	19/32	0.59	11/18	0.61
02W	Menomune	6/31	0.19	25/27	0.93
	TetraMenD	3/34	0.09	24/27	0.89
09W	Menomune	8/39	0.20	8/11	0.73
	TetraMenD	8/40	0.20	9/10	0.90

(g) BR ? 1:128 vs HC ? 1:4 at day 28

Study	Vaccine	BR+ within HC+	Sensitivity	BR- within HC-	Specificity
02A	Menomune	50/50	1.00	0/2	0.00
	TetraMenD	47/47	1.00	0/3	0.00
02C	Menomune	70/70	1.00	2/11	0.18
	TetraMenD	79/79	1.00	0/5	0.00
02Y	Menomune	59/59	1.00	1/3	0.33
	TetraMenD	60/61	0.98	0/4	0.00
09Y	Menomune	49/50	0.98	0/0	?
	TetraMenD	47/48	0.98	0/2	0.00
02W	Menomune	53/54	0.98	0/4	0.00
	TetraMenD	60/60	1.00	0/1	0.00
09W	Menomune	50/50	1.00	0/0	?
	TetraMenD	50/50	1.00	0/0	?

(h) BR ? 1:128 vs HC ? 1:8 at day 28

Study	Vaccine	BR+ within HC+	Sensitivity	BR- within HC-	Specificity
02A	Menomune	46/46	1.00	0/6	0.00
	TetraMenD	40/40	1.00	0/10	0.00
02C	Menomune	62/62	1.00	2/19	0.10
	TetraMenD	77/77	1.00	0/7	0.00
02Y	Menomune	59/59	1.00	1/3	0.33
	TetraMenD	60/61	0.98	0/4	0.00
09Y	Menomune	49/50	0.98	0/0	?
	TetraMenD	47/48	0.98	0/2	0.00
02W	Menomune	52/53	0.98	0/5	0.00
	TetraMenD	58/58	1.00	0/3	0.00
09W	Menomune	49/49	1.00	0/1	0.00
	TetraMenD	49/49	1.00	0/1	0.00

(i) BR ? 1:256 vs HC ? 1:4 at day 28

Study	Vaccine	BR+ within HC+	Sensitivity	BR- within HC-	Specificity
02A	Menomune	47/50	0.94	0/2	0.00
	TetraMenD	47/47	1.00	0/3	0.00
02C	Menomune	69/70	0.98	3/11	0.27
	TetraMenD	73/79	0.92	0/5	0.00
02Y	Menomune	59/59	1.00	1/3	0.33
	TetraMenD	58/61	0.95	1/4	0.25
09Y	Menomune	44/50	0.88	0/0	?
	TetraMenD	45/48	0.98	0/2	0.00
02W	Menomune	51/54	0.94	1/4	0.25
	TetraMenD	56/60	0.93	0/1	0.00
09W	Menomune	50/50	1.00	0/0	?
	TetraMenD	49/50	0.98	0/0	?

(j) BR ? 1:256 vs HC ? 1:8 at day 28

Study	Vaccine	BR+ within HC+	Sensitivity	BR- within HC-	Specificity
02A	Menomune	45/46	0.98	2/6	0.33
	TetraMenD	40/40	1.00	0/10	0.00
02C	Menomune	61/62	0.98	3/19	0.16
	TetraMenD	71/77	0.92	0/7	0.00
02Y	Menomune	59/59	1.00	1/3	0.33
	TetraMenD	58/61	0.95	1/4	0.25
09Y	Menomune	44/50	0.88	0/0	?
	TetraMenD	45/48	0.94	0/2	0.00
02W	Menomune	50/53	0.94	1/5	0.20
	TetraMenD	54/58	0.93	0/3	0.00
09W	Menomune	49/49	1.00	0/1	0.00
	TetraMenD	48/49	0.98	0/1	0.00

2.5. Reviewer's Overall Comments for SBA-BR and SBA-HC

1. From the first two tables, comparisons of the criteria of BR ? 4-fold rise with HC ? 1:4 and HC ? 1:8 at day 28, indicate that the sensitivity results are mostly above 80%. However, the specificity results are mostly around 0%. Although this could be due to the small number of subjects who were not seroprotected as defined by HC assays, these results nonetheless do not provide enough evidence that BR titer ? 4-fold rise should be used as an alternative definition of seroprotection with the current data.

2. Further exploratory analyses were performed by the reviewer to compare the possible alternative definitions such as BR ? 1:128 or BR ? 1:256. The comparisons were made at both day 0 and day 28. In general, the sensitivities and specificities are both higher for day 0 (indicating greater similarity of the two methods) but specificities are very low for day 28 (indicating disagreement).

3. Although an individual clearly responds differently with the two assays (BR and HC), the responses of the two groups with different vaccines appear to be 'similar' within each assay method. However, these studies were not sufficiently powered to permit drawing a definitive conclusion. A study of larger sample size may provide more information on the relationship between the two assay methods.

4. From the seroprotection rate and ANCOVA analyses in comparing the two assay methods, the conclusions reached by using the criteria of BR titer ? 4-fold rise do not contradict those drawn using the criteria of HC titers. Therefore, it may be accepted as a method for judging non-inferiority of immunogenicity of the investigational , TetraMenD to the licensed Menomune but not as an alternative definition of seroprotection.

3. Clinical Studies Performed by AP

Table 3.1: Summary of Clinical Studies in the TetraMenD Program and Age and Number of Participants in Each Study

Study Number	Type of Study	Number of Injections/ Vaccination Schedule	Age of Population	Enrolled to receive TetraMenD	Enrolled to receive Menomune®
603-01	Dose Escalation	1 vaccination (Day 0)	18 to 55 yrs	**30***	None
MTA02	Safety & Immunogenicity Comparison of TetraMenD versus Menomune®	1 vaccination (Day 0)	11 to 18 yrs	**440**	**441**
MTA04	Safety Comparison of TetraMenD versus Menomune®	1 vaccination (Day 0)	11 to 18 yrs	**2270**	**972**
MTA09	Safety & Immunogenicity Comparison of TetraMenD versus Menomune®	1 vaccination (Day 0)	18 to 55 yrs	**1384**	**1170**
MTA14	Consistency of Immunogenicity of TetraMenD and Safety Comparison of TetraMenD versus Menomune®	1 vaccination (Day 0)	18 to 55 yrs	**1582**	**458**
MTA12	Safety & Immunogenicity of Concomitant Administration of TetraMenD with Tetanus Diphtheria Combined Vaccine	2 vaccinations Group A: Td + TetraMenD (Day 0) and Placebo (Day 28) Group B: Td + Placebo (Day 0) and TetraMenD (Day 28)	11† to 17 yrs	**1021** 509 512	None
MTA11	Safety & Immunogenicity of Concomitant Administration of TetraMenD with Typhoid Vi® Vaccine	2 vaccinations Group A: Vi + TetraMenD (Day 0) and Placebo (Day 28) Group B: Vi + Placebo (Day 0) and TetraMenD (Day 28)	18 to 55 yrs	**945** 469 476	None
Total for all studies combined				**7672**	**3041**

* A group (each) of 30 adult participants also received a 1 µg dose and a 10 µg dose of TetraMenD in this study

† One participant was enrolled prior to turning 11 years old, and is included as an 11-year-old in the analyses.

Reference: ISS, Section 11, Table 1.0 and Table 3.0

3.1 Reviewer's Comments

1. The non-inferiority with respect to immunogenicity of TetraMenD compared to Menomune, using the 4-fold rise in SBA-BR complement, has been demonstrated in studies MTA02 for 11-18 years olds and MTA09 for 18 -55 years olds.

2. There are no statistical concerns regarding studies 603-01, MTA02, MTA04, MTA09, MTA12, and MTA11.

3. In study MTA14, the primary objective is to demonstrate lot consistency of 3 lots of the investigational vaccine, TetraMenD.

   The primary hypothesis:
   Twenty-eight days after vaccination, the immune responses elicited by the three consistency lots of TetraMenD, as measured by the geometric mean titer (GMT), are equivalent for each of the four serogroups.

   This hypothesis will be supported by the data if the upper limit of the two-sided 90% confidence interval of the difference between the maximum and the minimum effect among the three lot responses is $< \log_2(1.5)$; these effects are estimated by analysis of covariance of the log base 2 of the response at Day 28. In order to avoid disparities between groups due to imbalanced baseline titer, responses at Day 28 are adjusted by subtracting the responses at baseline and using the baseline as one of the covariates.

   Results submitted by AP from study MTA14 are listed in the following table. These results have been verified by the reviewer. Note that for serogroups C and Y, the upper limits of the 90% confidence intervals have exceeded the pre-determined value of 1.5.

Table 5.31: SBA-BR GMT Difference on Day 28 due to Treatment and Upper Limit of Two Sided 90% CI of Difference in Treatment Effect, Primary Hypothesis (Per-Protocol Population)

SBA Serogroup/TetraMenD Lot	Difference of Treatment Effect (Max-Min)	Anti-Log of Treatment Effect (Max-Min)	Upper Limit of the Two-Sided 90% CI for Anti-Log of Treatment Effect
Serogroup A			
Lot 1, Lot 2, Lot 3	0.297	1.228	1.390
Serogroup C			
Lot 1, Lot 2, Lot 3	0.459	1.375	1.637
Serogroup Y			
Lot 1, Lot 2, Lot 3	0.579	1.493	1.734
Serogroup W-135			
Lot 1, Lot 2, Lot 3	0.334	1.261	1.491

Reference: Section 9, Table 9.51 and Appendix 16, Listing 23.

4. Reviewer's Summary Comments

1. The criterion of at least a 4-fold rise at day 28 after the vaccination by the serum bactericidal assay with the baby rabbit complement (SBA-BR) appears acceptable as a method for non-inferiority immune comparability for the 11-55 age group, but not acceptable as an alternative measure for definition of seroprotection unless more definitive evidence is provided.

2. The results of the clinical trials demonstrated non-inferiority (with respect to immunogenicity) of TetraMenD compared to Menomune by the SBA-BR method for the11-55 age group.

3. The results of the lot consistency evaluation indicate that serogroups C and Y did not meet the primary objective of the predefined equivalence limit of 1.5 for the GMT ratios. The C and Y values 1.637 and 1.734, respectively, are within a 2-fold difference.

Appendix

Figure 9: MTA02 - Reverse Cumulative Distribution Curves of SBA-HC Titers (Subset Population) on Day 0 for Serogroup C

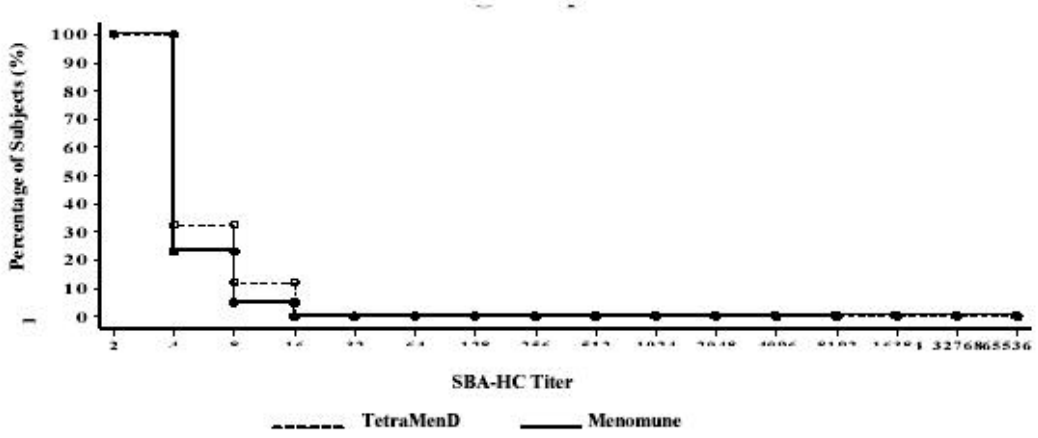

Figure 11: MTA02 - Reverse Cumulative Distribution Curves of SBA-BR Titers (Subset Population) on Day 0 for Serogroup C

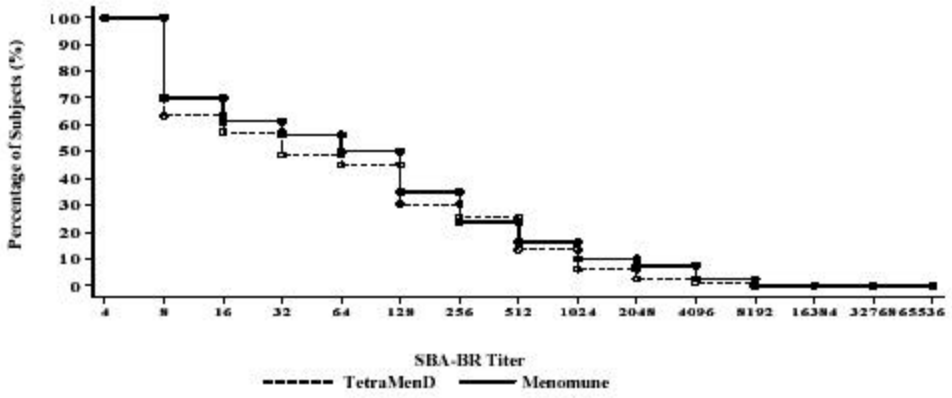

Figure 10: MTA02 - Reverse Cumulative Distribution Curves of SBA-HC Titers (Subset Population) on Day 28 for Serogroup C

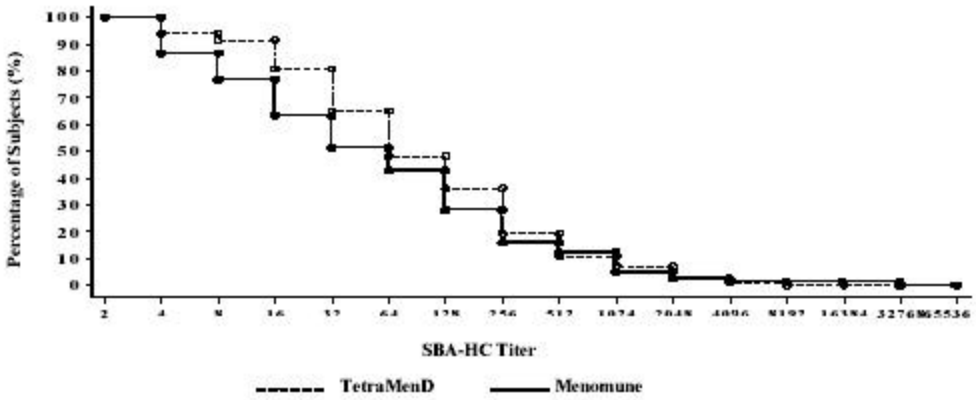

Figure 12: MTA02 - Reverse Cumulative Distribution Curves of SBA-BR Titers (Subset Population) on Day 28 for Serogroup C

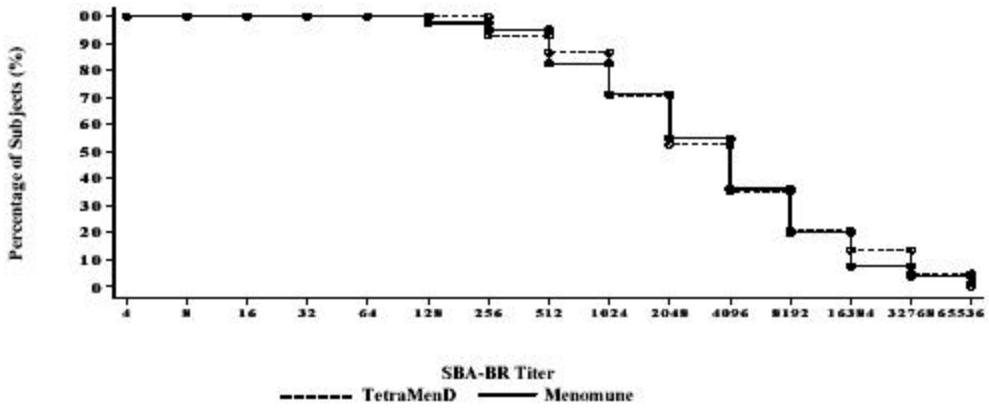

Figure 13: MTA02 - Reverse Cumulative Distribution Curves of SBA-HC Titers (Subset Population) on Day 0 for Serogroup Y

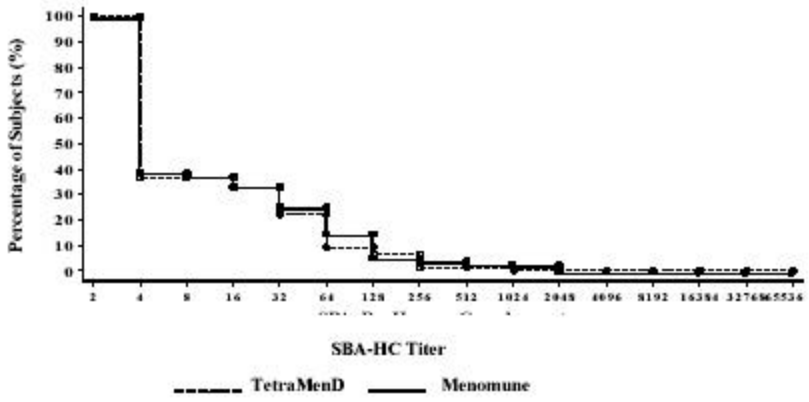

Figure 15: MTA02 - Reverse Cumulative Distribution Curves of SBA-BR Titers (Subset Population) on Day 0 for Serogroup Y

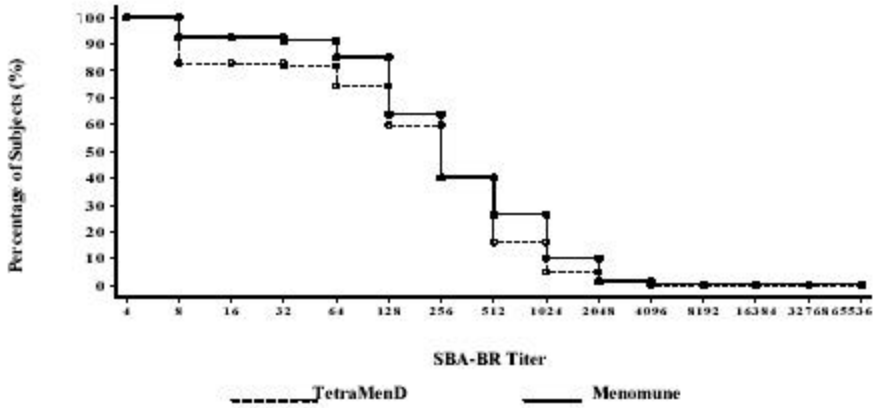

Figure 14: MTA02 - Reverse Cumulative Distribution Curves of SBA-HC Titers (Subset Population) on Day 28 for Serogroup Y

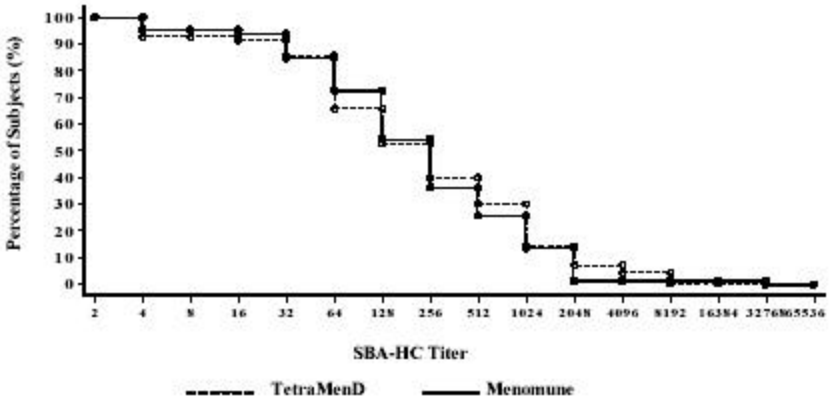

Figure 16: MTA02 - Reverse Cumulative Distribution Curves of SBA-BR Titers (Subset Population) on Day 28 for Serogroup Y

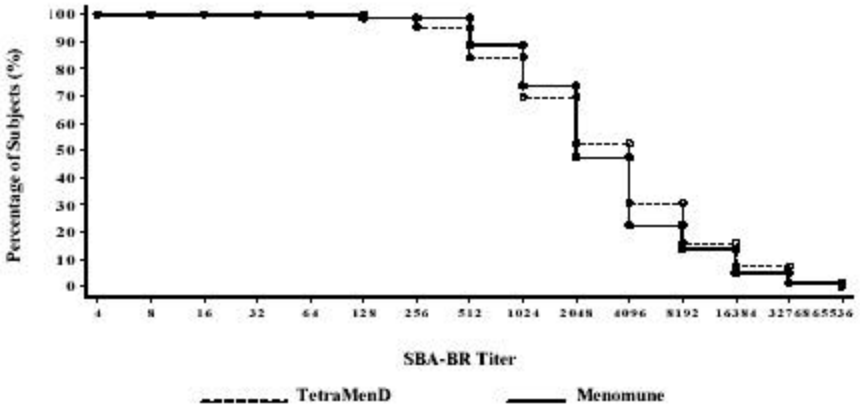

Figure 17: MTA02 - Reverse Cumulative Distribution Curves of SBA-HC Titers (Subset Population) on Day 0 for Serogroup W135

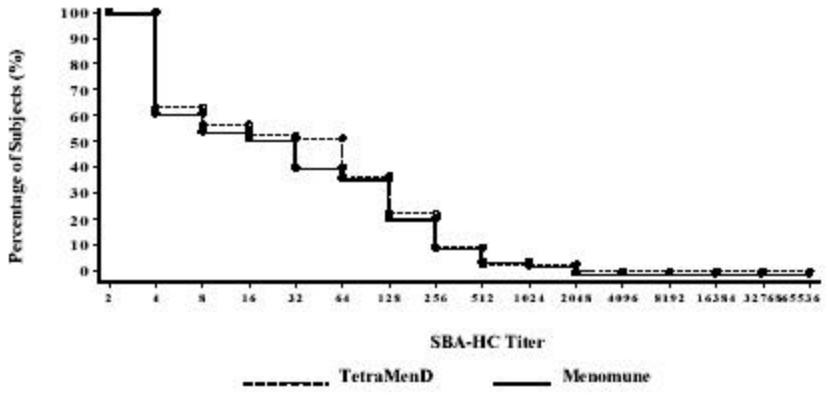

Figure 19: MTA02 - Reverse Cumulative Distribution Curves of SBA-BR Titers (Subset Population) on Day 0 for Serogroup W135

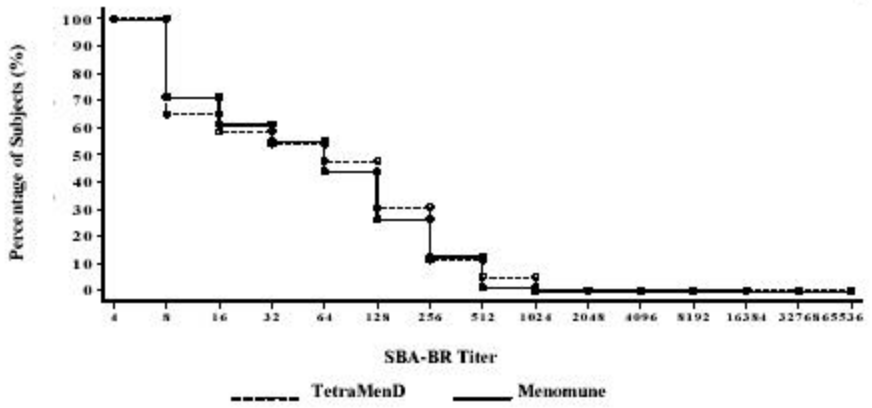

Figure 18: MTA02 - Reverse Cumulative Distribution Curves of SBA-HC Titers (Subset Population) on Day 28 for Serogroup W135

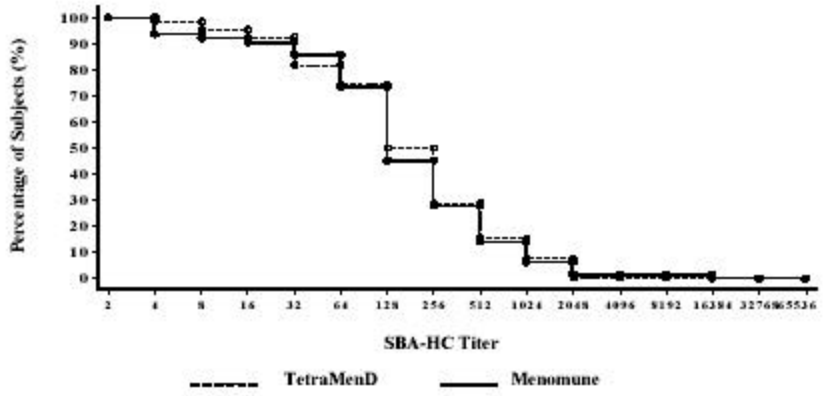

Figure 20: MTA02 - Reverse Cumulative Distribution Curves of SBA-BR Titers (Subset Population) on Day 28 for Serogroup W135

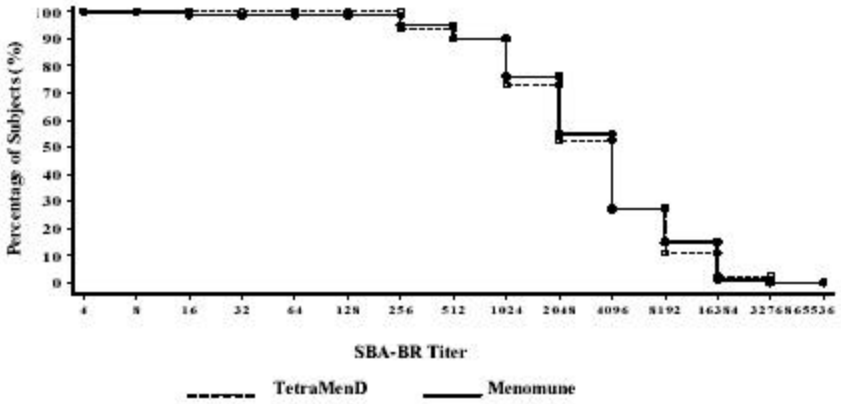

Figure 29: MTA09 - Reverse Cumulative Distribution Curves of SBA-HC Titers (Subset Samples) on Day 0 for Serogroup Y

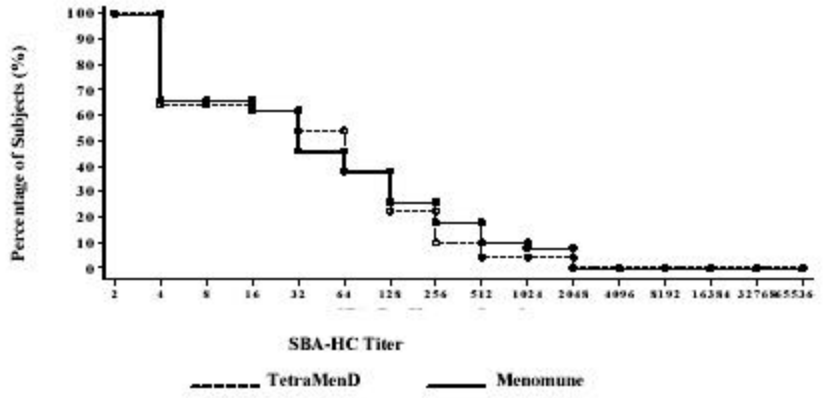

Figure 31: MTA09 - Reverse Cumulative Distribution Curves of SBA-BR Titers (Subset Samples) on Day 0 for Serogroup Y

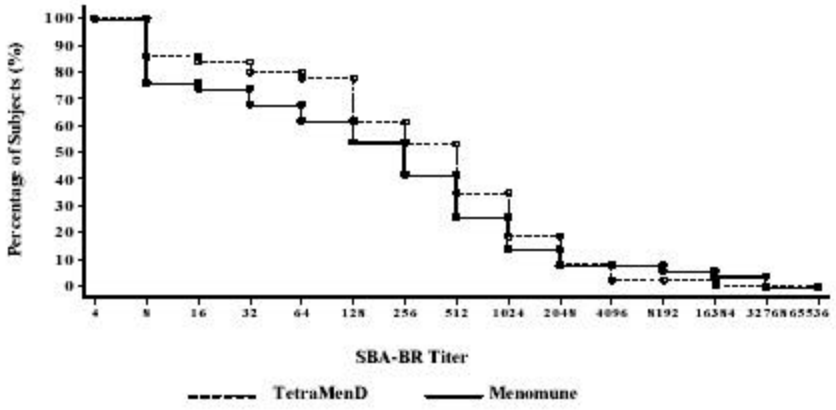

Figure 30: MTA09 - Reverse Cumulative Distribution Curves of SBA-HC Titers (Subset Samples) on Day 28 for Serogroup Y

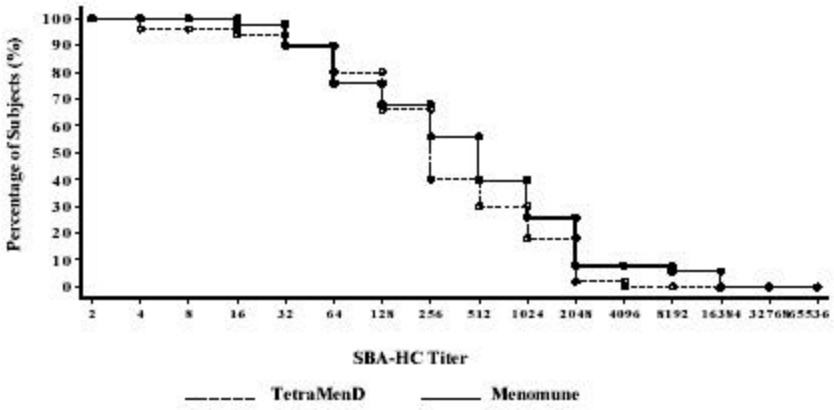

Figure 32: MTA09 - Reverse Cumulative Distribution Curves of SBA-BR Titers (Subset Samples) on Day 28 for Serogroup Y

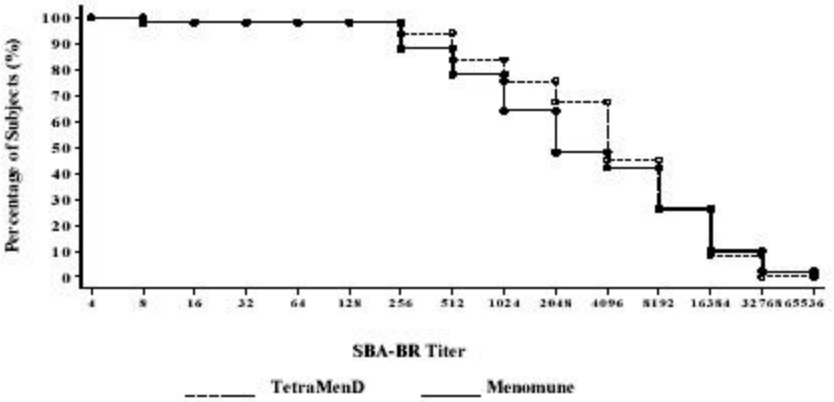

Figure 33: MTA09 - Reverse Cumulative Distribution Curves of SBA-HC Titers (Subset Samples) on Day 0 for Serogroup W135

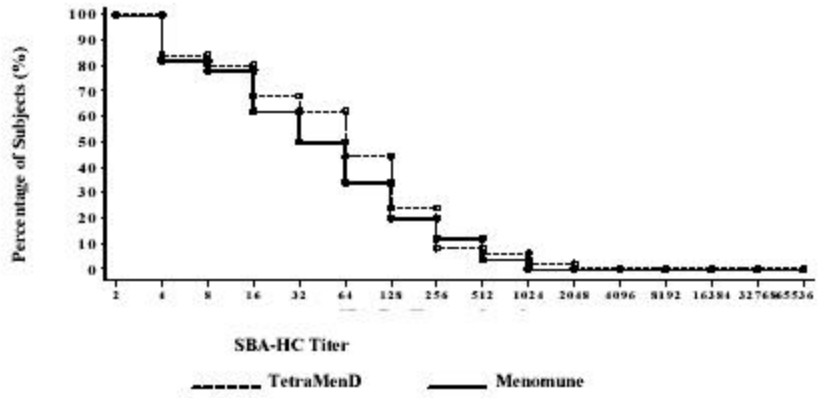

Figure 35: MTA09 - Reverse Cumulative Distribution Curves of SBA-BR Titers (Subset Samples) on Day 0 for Serogroup W135

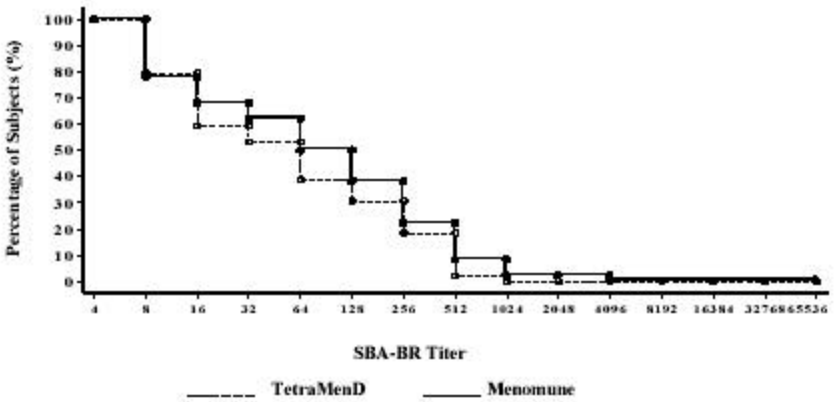

Figure 34: MTA09 - Reverse Cumulative Distribution Curves of SBA-HC Titers (Subset Samples) on Day 28 for Serogroup W135

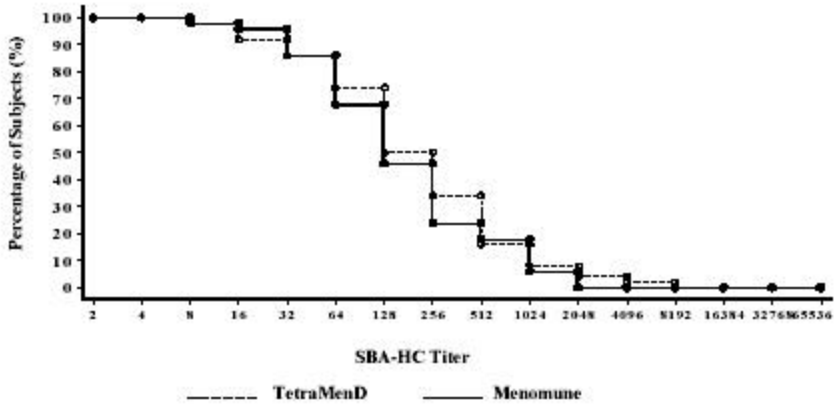

Figure 36: MTA09 - Reverse Cumulative Distribution Curves of SBA-BR Titers (Subset Samples) on Day 28 for Serogroup W135

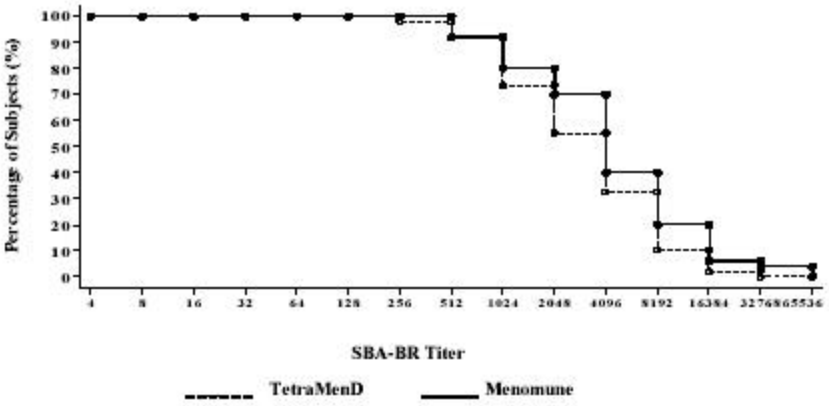

Figure 1: MTA02 - Reverse Cumulative Distribution Curves of SBA-HC Titers (Subset Population) on Day 0 and Day 28 for Serogroup A

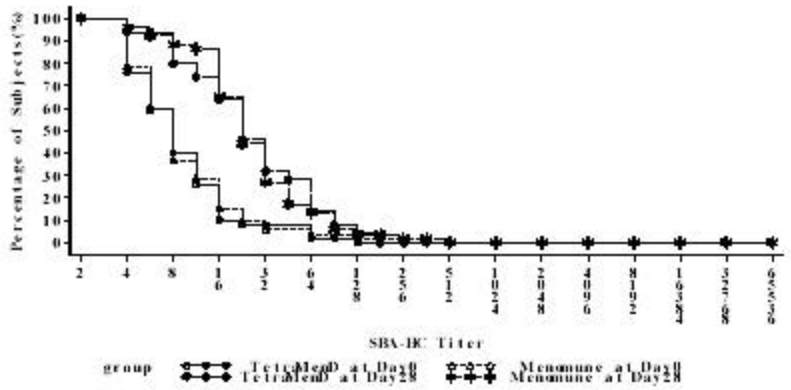

Figure 2: MTA02 - Reverse Cumulative Distribution Curves of SBA-BR Titers (Subset Population) on Day 0 and Day 28 for Serogroup A